REMARKS

The Office Action and the cited and applied references have been carefully reviewed. No claim is allowed. Claims 1-15 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

Claims 1-3 have been rejected under 35 U.S.C. §103(a) as being anticipated by Minami et al. The examiner states that Minami administers aminoguanidine and the L-arginine analog, NG-nitro-L-arginine methyl ester (L-NAME), which is a non-isozyme selective NOS inhibitor. This rejection is obviated by the amendment to claim 1 to recite that the NOS-3 regulating agent is "selective for the nitric oxide synthase-3 (NOS-3) isoform" as fully supported by the specification at page 15, lines 17-23. Aminoguanidine was used by Minami as a competitive inhibitor of inducible NO synthase (iNOS, also known as NOS-2). Neither L-NAME nor aminoguanidine is selective for the NOS-3 isoform. Accordingly, Minami cannot anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1-6 and 8 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Minami et al. (1998), taken in view of Poduslo et al. (U.S. Patent no. 5,670,477). This rejection is respectfully traversed.

Minami teaches at page 38, bottom of right column, that:

> The finding that aminoguanidine, a competitive inhibitor of iNOS, inhibits the penetration of fluorescein into the brain of the LPS-treated mice, suggests that NO produced by iNOS injures BBB. (emphasis added)

Inducible NOS (iNOS), which is also known as NOS-2, is different from the NOS-3 (endothelial NOS) isoform. There is no disclosure or teaching whatsoever in Minami that would lead one of ordinary skill in the art to administer a selective NOS-3 inhibitor (not a NOS-2 inhibitor or a non-selective NOS inhibitor), as presently recited in the claims, for the purpose of reducing the increased permeability of the BBB. The disclosures and teachings of Poduslo do not satisfy the deficiency in Minami. Rather, Poduslo would lead one of ordinary skill in the art further astray from the presently claimed invention.

Poduslo teaches the use of carrier molecules, which have substantial permeability across the BBB, to enhance the ability of neurologically active compounds to penetrate the BBB. However, such use of permeable carrier molecules does not affect the permeability of the BBB, i.e., disrupt the BBB, because the BBB is still intact. Furthermore, Poduslo's goal is to penetrate the BBB, whereas the use of inhibitors in Minami is for the purpose of reducing the permeability of the BBB caused by damage that is induced by LPS.

Accordingly, neither Minami nor Poduslo, alone or in combination, can lead one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 1, 4, 6, 7, and 9-15 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Barna et al (1996), taken in view of Friden (U.S. Patent no. 5,527,527). This rejection is respectfully traversed.

While Barna discloses that administration of IL-12, IFN-γ or TNF-α increases NOS-3 expression, there is no teaching in Barna that this leads to an increase in the permeability of the BBB. There is only the conjecture in Barna at page 340 that:

> The increased expression of type III NOS in astrocytes may be a contributory factor of VSV-associated BBB disruption.

Even if one were to jump to the conclusion based on conjecture in Barna that the increased expression of NOS-3 may be a contributory factor of VSV-associated BBB disruption, there is simply no motivation for one of ordinary skill in the art to cause increased disruption to the BBB, i.e., general permeability, much like in a VSV viral infection that causes damage to the BBB. The applied Friden reference teaches delivery of therapeutic agents using carriers that are permeable to the BBB. It is clear that Friden teaches away from a general increase in the permeability of the BBB, which is a disruptive event, and instead teaches that therapeutic agents are carried across the BBB while maintaining the normal

permeability or *status quo* of the BBB. Maintenance of the BBB appears to be an objective in the studies of Barna et al. Therefore, it would be quite unobvious to one of ordinary skill in the art to cause a disruptive viral infection-like event to the BBB for the express purpose of delivering a therapeutic agent in the face of the disclosures and teachings of Friden (and Poduslo) that enhanced delivery across the BBB can be achieved by using carriers with substantial permeability across the BBB without the need for any general disruption or increase in BBB permeability. Accordingly, Barna and Poduslo cannot lead one of ordinary skill in the art to the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

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